ISSN: 1607-8322, e-ISSN: 2220-5799 Anaesthesia, Pain & Intensive Care
Vol 26(5); October 2022 DOI: 10.35975/apic.v26i5.1990

ORIGINAL RESEARCH INTENSIVE CARE

A randomized study of an evaluation of Trigona honey as immunonutrition among ventilated pneumonia patients in intensive care unit

Rhendra Hardy Mohamad Zaini, MD, MMed[1], Sanihah Che Omar, MD, MMed[2], Isma Syarina Binti Ismail, MD, MMed[3], Wan Mohd Nazaruddin Wan Hassan, MD, MMed[4], Praveena Seevaunnamtum, MD, MMed[5], Che Maraina Che Hussin, MD, MMed[6]

Author affiliations:

1. Rhendra Hardy Mohamad Zaini, Associate Professor, Department of Anesthesiology & Intensive Care, School of Medical Sciences & Hospital, Health Campus, Universiti Sains Malaysia (USM), 16150 Kubang Kerian, Kelantan, Malaysia; E -mail: rhendra@gmail.com
2. Sanihah Che Omar, Senior Lecturer, Department of Anesthesiology & Intensive Care, School of Medical Sciences & Hospital, Health Campus, Universiti Sains Malaysia (USM), 16150 Kubang Kerian, Kelantan, Malaysia.
3. Isma Syarina Binti Ismail, Department of Anesthesiology & Intensive Care, School of Medical Sciences & Hospital, Health Campus, Universiti Sains Malaysia (USM), 16150 Kubang Kerian, Kelantan, Malaysia; E -mail: isma_syarina@yahoo.com
4. Wan Mohd Nazaruddin Wan Hassan, Associate Professor, [5]Department of Anesthesiology & Intensive Care, School of Medical Sciences & Hospital, Health Campus, Universiti Sains Malaysia (USM), 16150 Kubang Kerian, Kelantan, Malaysia; E -mail: nazarudin@usm.my
5. Praveena Seevaunnamtum, Senior Lecturer, Department of Anesthesiology & Intensive Care, School of Medical Sciences & Hospital, Health Campus, Universiti Sains Malaysia (USM), 16150 Kubang Kerian, Kelantan, Malaysia; E -mail: praveenaseeva@usm.my
6. Che Maraina Che Hussin, Associate Professor, Department of Immunology, School of Medical Sciences, Health Campus, University Sains Malaysia (USM), 16150, Kubang Kerian, Kelantan, Malaysia; E-mail: maraina@usm.my

Correspondence: Sanihah Che Omar, Tel: +60122159484; Fax: +6097653370; E-mail: sanihah_che@usm.my

Abstract

Background & Objective: Honey is one of the traditional drugs and has been widely used as a nutrient supplement for centuries. It is known to have antimicrobial, antioxidant and radical scavenging properties. We aimed to prove that natural honey can be added as a supplementary nutrient for its immunoprotective effects to the ventilated pneumonia patients in intensive care unit (ICU).

Methodology: A total of 40 ventilated pneumonia patients were randomized to receive enteral feeding with honey (n = 20) or without honey (n = 20). A bolus of 20 g of honey was given every day for 5 days together with normal enteral nutrition. The baseline vital signs, ventilator settings, blood samples for C-reactive protein (CRP), white blood cell (WBC), interleukin-6 (IL-6), interleukin-10 (IL-10), immunoglobulin A (IgA) and blood sugar level were taken on the day of recruitment (Day 0) and subsequently on Day 3 and Day 6.

Results: There were significant changes in IL-6 level over time in honey group with mean decrease of IL-6 from 265.1 pg/ml on Day 0 to 101.8 pg/ml on Day 6 ($P < 0.001$). There was no significant effect on CRP ($P = 0.22$), IL-10 ($P = 0.548$), IgA ($P = 0.197$), WBC count ($P = 0.640$) and blood sugar level between both groups ($P > 0.05$). Duration of antibiotic use between the two groups showed no statistically significant difference with $P = 0.075$ and length of ICU stay.

Conclusion: Trigona honey showed the beneficial effect of immunonutrition to ventilated pneumonia patients in ICU by significantly decreasing the level of IL-6.

Abbreviations: CAP: community acquired pneumonia; CRP: C-reactive protein; DHA: docosahexaenoic acid; HAC: hospital acquired pneumonia; ICU: intensive care unit; IL-6: interleukin-6; Ig-A: immunoglobulin A; NGT: Nasogastric tube; RBS: random blood sugar; VAP: ventilator associated pneumonia

Key words: Trigona Honey; Pneumonia; Interleukin-6; Interleukin-10; Immunonutrition

Citation: Zaini RHM, Omar SC, Binti Ismail IS, Wan Hassan WMN, Seevaunnamtum P, Che Hussin CM. A randomized study of an evaluation of Trigona honey as immunonutrition among ventilated pneumonia patients in intensive care unit. Anaesth. pain intensive care 2022;26(5):649-655; **DOI:** 10.35975/apic.v26i5.1990

Received: December 16, 2021; **Reviewed:** June 29, 2022; **Accepted:** July 20, 2022

1. Introduction

Pneumonia is the one of the main diagnoses on admission to Intensive Care Unit (ICU) worldwide and is one of the top five causes of death in Malaysia.[1] It can be community acquired pneumonia (CAP), hospital acquired pneumonia (HAP) or ventilator associated pneumonia (VAP). Many studies and reviews have been done regarding pneumonia in order to produce better prognostic tools, as well as treatment and management strategies for pneumonia as the disease leads to a high mortality of about 1 per 1000 cases.[2,3]

Almost all patients in ICU will experience myopathy complication, it can be due to disease, drugs or rehabilitation.[4] It can occur during the critical phase of infection as well as during the recovery phase, but can be improved by avoiding unnecessary drugs and with good rehabilitation. Rehabilitation, involves not only physical activity, but nutrition also plays an important role in it.

Malnutrition has been reported to be between 30% and 55% in the hospitalized patients,[5] and it is known to be associated with increased morbidity and mortality, particularly among patients admitted to an ICU. In 'Latin America Nutrition' a study that involved multicentre epidemiological study, enrolled 9348 hospitalized patients. It revealed that malnutrition was present in 50.2% of the patients studied. Severe malnutrition was present in 11.2% of the entire group. Malnutrition correlated with age (> 60 y), presence of cancer and infection, and longer length of hospital stay ($P < 0.05$).[6] Patients hospitalized for pneumonia frequently suffered from malnutrition due to hypermetabolic state. Prolonged ventilator dependency as a result of failing to restore respiratory muscle strength and endurance could be due to malnutrition. According to Journal of Nutrition and Food Sciences, immunonutrition has the potential to modulate the activity of the immune system by interventions with specific nutrients.[7,8]

The nutrients given in supranormal amount are beneficial to the patients with hypermetabolic state. The basic aims are to modulate the immune response with naturally occurring nutrients so as to limit tissue injury, reduce infection rates and morbidity, ultimately improving survival rate. A study done by DeWitt RC et al. concluded that addition of 2% glutamine to total parenteral nutrition preserves immunity in the respiratory tract and reduces mortality to a lethal bacterial challenge compared with standard total parental nutrition (TPN).[9]

Honey has been used for ages due to its health benefits. It has been used topically as well as a part of food. Studies have been conducted to describe its use to treat illness and infections.[10,11] However, its effects on the respiratory and immune system have not been extensively studied. Trigona honey has been produced by small-sized, stingless honey bee, so its breeding is easy at home.

We conducted this study to prove that natural honey can be added as a supplementary nutrient for the ventilated pneumonia patients in ICU, with positive effects on immune system and respiratory function.

2. Methodology

This prospective, single blinded, randomized trial was approved by the Institutional Research & Ethics Committee (approval code: USM/JPEeM/17100425). This administration of the study items was carried out at the ICU by the-nurses incharge of the patients who had at least 2 y of experience working in ICU. Eligible patients, recruited in the study were explained and written informed consent obtained from them or their guardians.

The inclusion criteria were pneumonia (CAP/HAP/VAP), ventilated patients with evident of a new infiltrate on chest radiograph, and persistent (48 h plus) 2−3 criteria; e.g., white blood cell count ≥ 12 x 109/ L, temperature > 38ºC, purulent tracheobronchial secretion or cultures positive for microorganisms causing CAP/HAP/VAP. Others inclusion criteria were age between 18–65 y and expected survival of up to 6 days with Acute Physiology and Chronic Health Evaluation (APACHE) score < 25.

The exclusion criteria included history of allergy to honey, intestinal obstruction, upper gastrointestinal bleed, malnutrition or severe obesity (body mass index < 18.5 or > 35 kg/m^2, immunocompromised, pregnant and lactated ladies, severe shock requiring high dose of inotropic supports (> 1 inotrope), ARDS patients with high ventilator setting (P:F < 200).

Patient were randomized into two groups; Honey group (Group A) with standard enteral feeding formula milk plus Trigona honey and Non-honey group (Group B) with standard enteral feeding formula milk only, using

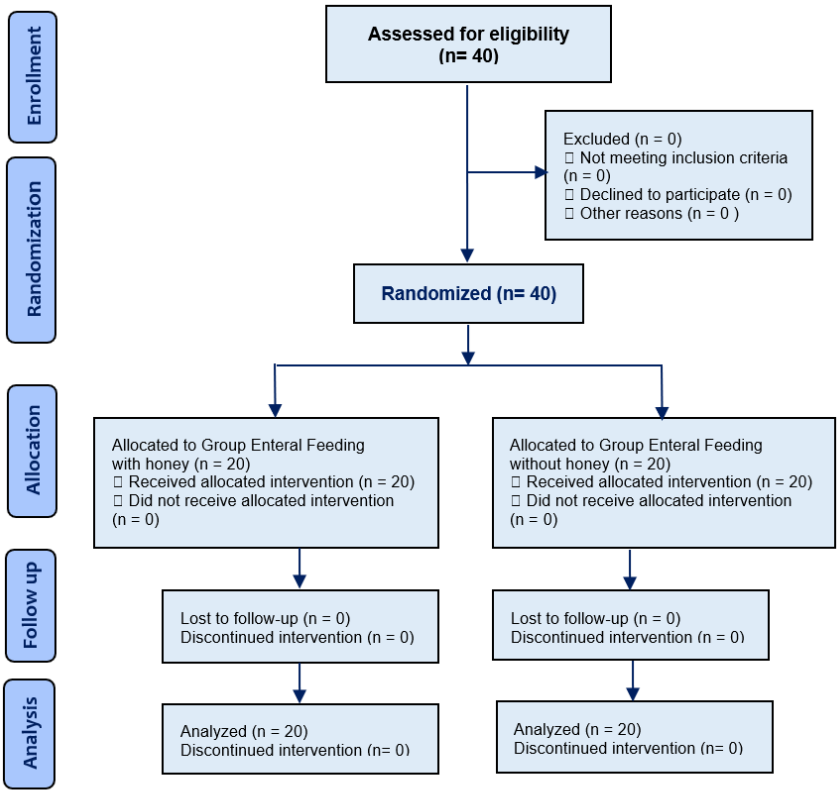

Figure 1: CONSORT flowchart of patient selection

computer-generated random tables to ensure allocation concealment. All patients with documented CAP, HAP or VAP commenced empirical antibiotic therapy on the day of bacteriological culture. When bacteriological results were available, antibiotics were changed according to the pathogens isolated and the antimicrobial susceptibility test results.

Nasogastric tube (NGT) was inserted and its correct placement confirmed. Enteral feeding (Ensure®, Glucerna®, Peptamen® or other standard enteral formulation) was started. The enteral feeding was delivered by a pump for 24 h a day; started at 10–40 ml/h, and advance by 10-20 ml every 8 – 12 h (Lord L et al., 1988) till the maximum dose based on the required calories was reached. The standard enteral feeding plus 20 g Trigona honey was freshly prepared by designated company and labelled with patient and study number, the name of the investigator, and date of preparation.

Group A received standard enteral feeding plus Trigona Honey (20 g) once a day for 5 consecutive days. Group B was given standard enteral feeding based on our ICU protocol (see appendix). After feeding, all patients were placed in the semi-recumbent position with the head of the bed elevated to 45°. The assessment of feeding tolerance was carried out every 4 h. The baseline vital signs, ventilator setting, blood samples for C-reactive protein (CRP), white blood cells (WBC), interleukin-6 (IL-6), interleukin-10 (IL-10), immunoglobulin A (IgA) and blood sugar levels were drawn on the day of recruitment (Day 0), Day 3 and Day 6 and sent to the laboratory on the same day. Apart from that, samples for blood culture and endotracheal tube cultures were also drawn on the Day 0. Antibiotic usage and the length of ICU stay were noted. Data from both groups were then compared and analyzed. Started from the enrollment into the study, all patients were observed for any reactions or complications such as allergy reaction, anaphylaxis or any adverse reactions. The patients remained blinded to the treatment allocation until the final statistical evaluation was completed.

Statistical analysis

The sample size was calculated using G*Power version 3.1 software. Considering the power of 80% and the type 1 error α of 5%, the sample size required was 18 participants in each group. Ten per cent was added for the dropouts. Therefore, the sample size was 20 participants for each group.

The statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) software version 24.0 (SPSS Inc, USA). For the numerical data analysis such as social demographic, ventilator setting and hemodynamics, we used the independent t-test (continuous response measures in two groups) or Mann-Whitney test with a P value of 0.05 and power of 0.8. Each null hypothesis was tested with respect to a two-sided alternative hypothesis. As for data that results where the outcome variable takes only two values such as yes or no, such as ETT culture, blood culture, and antibiotic usage, we used the dichotomous chi-square analysis (independent prospective of two proportion) or fisher's exact test where each null hypothesis was tested with respect to a two-sided alternative hypothesis. Here the same P values of 0.05 and power of 0.8 was employed. A two-way repeated measure ANOVA (mixed-design) was used to determine whether there was a significant difference between honey group and control group in WBC, CRP, IL-6, IL-10, IgA and random blood sugar (RBS) levels, at three time-points (e.g., baseline, Day 3 and Day 6). Model assumptions of normality, homogeneity of covariance

Table 1: Demographic data (n = 40). Data given as Mean ± SD or n (%)

Variable	Non–honey (n = 20)	Honey (n = 20)	Mean difference (95% CI)	P-value[a]
Age (y)	52.8 ± 14.86	48.4 ± 15.96	-4.40 (-14.27, 5.66)	0.372[a]
Race				0.091[b]
• Malay	19.0 (57.6)	14 (42.4)		
• Non-Malay	1 (14.3)	6 (85.7)		
Weight (kg)	68.4 ± 10.14	67.0 ± 9.76	-0.50 (-6.87, 5.87)	0.875[a]
Height (cm)	165.4 ± 3.62	163.6 ± 7.01	-1.75 (-5.362, 1.86)	0.330[a]
Comorbid				0.038[b,d]
• No	3 (25.0)	9 (75.0)		
• Yes	17 (60.7)	11 (39.3)		
• HPT	1 (33.3)	2 (66.7)		
• DM	2 (50.0)	2 (50.0)		
• Lung	6 (100.0)	0 (0.0)		
• Others	7 (77.8)	2 (22.2)		
• Multiple	1 (16.7)	5 (83.3)		
Diagnosis				0.661[c,e]
• Community	2 (33.3)	4 (66.7)		
• Non-community	18 (52.9)	15 (47.1)		
• HAP	14 (66.7)	7 (33.3)		
• VAP	4 (30.8)	9 (69.2)		
ETT culture				0.736[b]
• Negative	15 (46.2)	7 (53.8)		
• Positive	14 (51.9)	13 (48.1)		
Blood culture				1.000[c]
• Negative	15 (48.4)	16 (51.6)		
• Positive	5 (55.6)	4 (44.4)		
APACHE Score	13.70 ± 3.62	9.70 ± 5.78	-4.00 (-7.99, -0.010)	0.049[a]

[a]Independent t-test; [b]Pearson Chi-Square; [c]Fisher's exact test; [d] P-value for Comorbid (Yes/No); [e]P-value for Diagnosis (community/non community); P < 0.05 statistically significant

and compound symmetry were checked. The significant level was taken at 0.05 as p-value.

3. Results

A total of 40 adult patients were recruited for this study after being screened and given consent by guardian or next of kin; and 20 patients were randomly allocated to one of the two groups. None of patients was excluded after the consent was signed.

The demographic profiles of the two groups were comparable (Table 1). During analysis, diagnosis was classified as CAP and non-CAP. In which HAP and VAP were included as non-CAP. Six patients were CAP, where 2 (33%) were in non-honey group and 4 (66.7%) were in the honey group. Thirty-three patients were diagnosed to be non-CAP, out of which 18 (52.9%) were in the non-honey group and 15 (47.1%) in the honey group (P = 0.661) between both groups. There was no significant difference between groups for blood and ETT culture (P > 0.05) (Table 1). There was significant difference in term of APACHE score between both groups (P = 0.049) (Table 1).

There were no significant differences in the means of the ventilator setting, fraction of inspired oxygen (FiO_2), positive end expiratory pressure (PEEP), partial pressure of oxygen (PaO_2) and ratio of the arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2, P/F ratio) with P > 0.05 between both groups (Table 2).

Efficacy of Honey

There were overall no significant changes in WBC over time (P = 0.108). There was no overall significant difference in the means of WBC between honey and non-honey groups with regards to time (P = 0.497). There was no significant interaction between groups and time in WBC level (P = 0.640) (Table 3).

There was no overall significant difference in the means of IL-6 level between honey and non- honey groups with regards to time (P = 0.248). There was a significant interaction between the groups and the time in the means of IL-6 level (P = 0.007). Therefore, stratification according to the group was done during data analysis.

For honey group, there was an overall significant change in IL-6 level over time (P < 0.001), where post-hoc paired t-test with Bonferroni correction showed significant decrease in between the mean IL-6 level on Day 0 and Day 6 (mean difference =163.3, 95% CI

Table 2: Comparison of mean ventilator setting between non- honey and honey group

Variable	Non–honey	Honey	Mean difference (95% CI)	P-value
FiO_2	0.4 (0.00)	0.4 (0.19)		0.279[b]
PEEP	7.8 (1.54)	7.4 (1.87)	0.450 (0.648, 1.548)	0.412[a]
PaO_2	139.5 (33.81)	142.7 (25.00)	-3.195 (-22.476, -16.086)	0.739[a]
P:F ratio	341.3 (101.88)[b]	381.0 (116.95)[b]		0.610[d]

[a]Independent t-test; normality and equal variances assumptions met
[b]median (IQR); [c]z-statistics; [d]Mann-Whitney test; P < 0.05 considered as statistically significant

Table 3: Comparison of the inflammatory level

Variable	Honey Group (n = 20)			Non–honey Group (n = 20)		
	Day 0	Day 3	Day 6	Day 0	Day 3	Day 6
WBC ($x10^9$ cell/L)	14.6 11.78, 17.38	19.3 8.64, 29.96	11.7 9.64, 13.89	17.8 3.63, 22.02	18.7 11.61, 25.78	14.5 11.61, 17.38
IL-6 (pg/ml)	265.1 137.74, 392.51	217.1 89.05, 345.08	101.8 29.05, 174.63	147.1 60.00, 234.13	141.1 49.03, 233.12	128.3 46.396, 210.376
IL-10 (pg/ml)	14.649 11.79, 7.5	19.296 8.64, 29.96	11.765 9.64, 13.89	17.8 13.63, 22.02	18.7 11.61, 25.78	14.491 11.61, 7.38
IgA (g/L)	2.213 1.80. 2.63	2.544 2.10, 2.99	2.462 1.99, 2.93	2.484 1.77, 3.20	2.298 1.51, 3.09	2.453 1.73, 3.18
CRP (mg/L)	140.100 111.42. 168.78	152.600 125.60. 179.60	119.200 88.09. 149.31	137.700 09.02. 166.38	114.800 87.80. 141.80	104.800 74.69. 134.91
RBS mmol/L	14.649 11.79-17.51	19.296 8.64-29.96	11.765 9.641-13.89	17.8 13.63-22.02	18.695 11.61-25.78	14.491 11.61-17.38

Repeated measure ANOVA was applied; Data given as Mean (95% Confidence Interval)

Table 4: Comparison of mean duration of antibiotic between non–honey and honey group

Variable	Median (IQR)		P value
	Non-honey group	Honey group	
Duration of antibiotic use (days)	7.5 (7.00)	14.0 (6.75)	0.075[c]

[c]Mann-whitney test; normality and equal variances assumptions not met
p < 0.05 is considered as statistically significant

:56.59, 269.92) (Table 3). For non-honey group, there was no overall significant changes in IL-6 over time (P = 0.809). There was no overall significant changes in IL-10 over time (P = 0.324). There was no significant difference in mean IL-10 with regards to time, (P = 0.956). There was no significant interaction between the groups and time in IL-10 (P = 0.548) (Table 3).

There was no overall significant changes in IgA over time (P = 0.702). There was no significant difference in mean IgA with regard to time (P = 0.989). There was no significant interaction between the groups and time in IgA (P = 0.197) (Table 3).

There was an overall significant change in CRP level over time (P = 0.032); however, post-hoc paired t-test with Bonferroni showed no significant change in the mean CRP level. There was no significant difference in mean CRP with regard to time (P = 0.263). There was no significant interaction between the groups and time in CRP (P = 0.229) (Table 3). RBS for both groups were

Table 5: Means of length of stay (day) among patients between groups over time

Variable	Non–honey Group	Honey Group	Mean difference (95% CI)	P-value
LOS (day)	23.4500 (17.92)	25.1500 (26.15)	-1.7 (-16.05. 12.65)	0.812a

[a]Independent t-test; normality and equal variances assumptions met
p < 0.05 considered statistically significant; Mean LOS was almost equal in both groups

observed for alternate days and analysis revealed that there was no significant difference in sugar control between the two groups (P > 0.05) (Table 3).

Duration of antibiotic showed no statistically significant (P = 0.075) between both groups (Table 4). No significant difference in length of ICU stay between both groups with P = 0.812. (Table 5).

4. Discussion

This study is one of the pioneer randomized trials evaluating Trigona Honey (*Madu Kelulut*) (TN) as immunonutrition for ventilated pneumonia patients in the ICU. Forty patients were recruited in this study. This study evaluated and compared the inter- and intra- group changes that occurred in several parameters when compared trigona honey (honey group) with non–honey group. The main finding of this study was the significant reduction in IL-6 level in honey group compared with the control group.

There was no significant difference (P > 0.05) in the demographic and related data, including age, race, weight, height, comorbidity, diagnosis, blood and ETT culture. The primary outcome of this study showed that Trigona honey significantly reduced the IL-6 level in the pneumonia patient compared to control group (P = 0.007). The reduction was observed between Day 0 and Day 6. This result is consistent with a previous study that revealed consumption of docosahexaenoic acid (DHA) rich fish oil and Tualang honey can be effective in lowering pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), IL-6, and interferon-gamma (IFN-γ) levels in the brains of rats under chronic stress conditions.[11] Another study also showed that honey (Gelam honey) could reduce edema in a dose-dependent fashion in inflamed rat paws, decrease in production of nitric oxide (NO), prostaglandin E2 (PGE2), TNF-α, and IL-6 in plasma, and suppress the expression of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), TNF-α, and IL-6 in paw tissue.[12]

Level of IL-10 showed no statistically significant difference between honey group and control group (P > 0.05). However, both groups showed reduction of IL-10 in similar manner. This result might be supported by a study that conducted by Popa et al.,[13] on rats that received honey with sulphonamides. The levels of IL-4, IL-6, IL-8, IL-10, vascular endothelial growth factor (VEGF), and many other cytokines were significantly increased compared with controls. IL-10 is the cytokine that protects the host from the organ injury, it acts by inhibiting other cytokines. So, the insignificant difference of reduction in IL-10 in this study showed that Trigona honey was not significantly suppressing the production of IL-10, which is good for the immunity of the patient in sepsis.

We found no significant changes in terms of reduction of WBC. The same result has been reported earlier in a study on patients taking probiotic (alone or plus honey) during pelvic radiotherapy.[14] This study was unable to show significant increment of IgA in between honey and control groups. An earlier study published in 2015 also showed no significantly changed serum IgA level in patients taking probiotic (alone or with honey) during pelvic radiotherapy.[14]

The CRP levels in this study showed no significant difference in reduction of CRP between both groups. Probably a longer time might be needed to suppress the CRP level. Few studies revealed reduction in CRP levels after one week and 30 days treatment with honey.[16.15]

There is no significant difference in types of antibiotic usage between both groups. However, these antibiotics were decided before enrolment of the patients into the study. Statistically significant difference in duration of antibiotic usage with longer duration has been observed in honey group. This finding has been contradicted with another study by Ranneh et al.[17] regarding trigona honey having strong antioxidant property. A few studies showed that honey has an antimicrobial property.[18,19]

There was no significant difference in sugar control between the groups. This showed that although honey contains sugar, still it has no clinical impact on sugar control.[20]

5. Conclusions

Our study concluded that Trigona honey suppresses the production of IL-6 which is one of the main cytokines, that plays a major role in inflammation and will cause cell damage in intubated pneumonia patients in ICU. By suppression of this cytokine, it hopefully can reduce the cell damage and shorten the duration of inflammation and infection. However, Trigona honey has no effect on

antibiotic usage, duration of antibiotic use and levels of WBC, CRP, IL-10 and IgA.

6. Data availability

The numerical data is available with the authors.

7. Acknowledgement

We gratefully thank the nursing staff and the Department of Clinical Pathology, Hospital USM, USM, 16150 Kubang Kerian, Kelantan, Malaysia.

8. Conflict of interest

The study utilized local resources of School of Medical Sciences & Hospital, and no external or industry funding was involved.

9. Authors' contribution

RHMZ, SCO: concept, design, execution, analysis, interpretation of the data, drafting and final approval of manuscript

ISI, WMNWH, SPS: CMCH: conception, design, critical revision and final approval of manuscript

10. References

1. Ministry of Health Malaysia: Health Facts; 2009. Available from: http://www.moh.gov.my/images/gallery/stats/heal_fact/healthfact-P_2009.pdf
2. Heffron R. Pneumonia, with special reference to pneumococcus lobar pneumonia (Vol. 12). Harvard University Press; 1979.
3. Garibaldi RA. Epidemiology of community-acquired respiratory tract infections in adults. Incidence, etiology, and impact. Am J Med. 1985 Jun 28;78(6B):32-7. [PubMed] DOI: 10.1016/0002-9343(85)90361-4
4. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med. 2002 Apr 1;165(7):867-903. [PubMed] DOI: 10.1164/ajrccm.165.7.2105078
5. Cerra FB, Lehmann S, Konstantinides N, Dzik J, Fish J, Konstantinides F, et al. Improvement in immune function in ICU patients by enteral nutrition supplemented with arginine, RNA, and menhaden oil is independent of nitrogen balance. Nutrition. 1991 May-Jun;7(3):193-9. [PubMed]
6. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med. 2014 Mar 27;370(13):1227-36. [PubMed] DOI: 10.1056/NEJMra1304623
7. Sulaiman SA, Hasan H, Deris ZZ, Wahab MS, Yusof RC, Naing NN. The benefit of Tualang honey in reducing acute respiratory symptoms among Malaysian hajj pilgrims: a preliminary study. J ApiProduct ApiMedical Sci. 2011;3(1):38-48. [FreeFullText]
8. Moore OA, Smith LA, Campbell F, Seers K, McQuay HJ, Moore RA. Systematic review of the use of honey as a wound dressing. BMC Complement Altern Med. 2001;1:2. [PubMed] DOI: 10.1186/1472-6882-1-2
9. Oddo LP, Heard TA, Rodríguez-Malaver A, Pérez RA, Fernández-Muiño M, Sancho MT, et al. Composition and antioxidant activity of Trigona carbonaria honey from Australia. J Med Food. 2008 Dec;11(4):789-94. [PubMed] DOI: 10.1089/jmf.2007.0724
10. Boorn KL, Khor YY, Sweetman E, Tan F, Heard TA, Hammer KA. Antimicrobial activity of honey from the stingless bee Trigona carbonaria determined by agar diffusion, agar dilution, broth microdilution and time-kill methodology. J Appl Microbiol. 2010 May;108(5):1534-43. [PubMed] DOI: 10.1111/j.1365-2672.2009.04552.x
11. Asari MA, Zulkaflee MH, Sirajudeen KNS, Mohd Yusof NA, Mohd Sairazi NS. Tualang honey and DHA-rich fish oil reduce the production of pro-inflammatory cytokines in the rat brain following exposure to chronic stress. J Taibah Univ Med Sci. 2019 Jul 23;14(4):317-323. [PubMed] DOI: 10.1016/j.jtumed.2019.06.004
12. Hussein SZ, Mohd Yusoff K, Makpol S, Mohd Yusof YA. Gelam Honey Inhibits the Production of Proinflammatory, Mediators NO, PGE(2), TNF-α, and IL-6 in carrageenan-induced acute paw edema in rats. Evid Based Complement Alternat Med. 2012;2012:109636. [PubMed] DOI: 10.1155/2012/109636
13. Popa ID, Şchiriac EC, Ungureanu D, Cuciureanu R. Immune response in rats following administration of honey with sulfonamides residues. Revista Română de Medicină de Laborator. 2012; 20(1/4). [FreeFullText]
14. Mansouri-Tehrani HA, Rabbani-Khorasgani M, Hosseini SM, Mokarian F, Mahdavi H, Roayaei M. Effect of supplements: Probiotics and probiotic plus honey on blood cell counts and serum IgA in patients receiving pelvic radiotherapy. J Res Med Sci. 2015 Jul;20(7):679-83. [PubMed] DOI: 10.4103/1735-1995.166224
15. Yaghoobi N, Al-Waili N, Ghayour-Mobarhan M, Parizadeh SM, Abasalti Z, Yaghoobi Z, et al. Natural honey and cardiovascular risk factors; effects on blood glucose, cholesterol, triacylglycerole, CRP, and body weight compared with sucrose. ScientificWorldJournal. 2008 Apr 20;8:463-9. [PubMed] DOI: 10.1100/tsw.2008.64
16. Soni N, Singh V, Mohammad S, Singh RK, Pal US, Singh R, et al. Effects of honey in the management of alveolar osteitis: A study. Natl J Maxillofac Surg. 2016 Jul-Dec;7(2):136-147. [PubMed] DOI: 10.4103/0975-5950.201354
17. Ranneh Y, Ali F, Zarei M, Akim AM, Hamid HA, Khazaai H. Malaysian stingless bee and Tualang honeys: A comparative characterization of total antioxidant capacity and phenolic profile using liquid chromatography-mass spectrometry. LWT. 2018;89:1-9. DOI: 10.1016/j.lwt.2017.10.020
18. Mandal MD, Mandal S. Honey: its medicinal property and antibacterial activity. Asian Pac J Trop Biomed. 2011 Apr;1(2):154-60. [PubMed] DOI: 10.1016/S2221-1691(11)60016-6
19. Efem SE, Udoh KT, Iwara CI. The antimicrobial spectrum of honey and its clinical significance. Infection. 1992 Jul-Aug;20(4):227-9. [PubMed] DOI: 10.1007/BF02033065
20. Bahrami M, Ataie-Jafari A, Hosseini S, Foruzanfar MH, Rahmani M, Pajouhi M. Effects of natural honey consumption in diabetic patients: an 8-week randomized clinical trial. Int J Food Sci Nutr. 2009 Nov;60(7):618-26. [PubMed] DOI: 10.3109/09637480801990389

